

Supporting information for Chang *et al.* (December 18, 2001) *Proc. Natl. Acad. Sci. USA*, 10.1073/pnas.012602599.

Table 2. Genes up-regulated in senescent relative to proliferating cell fractions in HCT116 cells separated after doxorubicin treatment (genes confirmed by RT-PCR are shown in boldface)

Gene name	Accession no.	Effects of*		Notes	BDE [‡]
		p53	p21		
Transcription factors					
X-box binding protein 1 (XBP-1/HTF/TREB)	AW021229			bZIP domain, c-Jun family, dimerizes with Fos (1)	3.9
Activating transcription factor 3 (ATF3)	N39944	↑ (2)		bZIP domain, dimerizes with c-Jun (3)	3.3
C-JUN	AI078377			AP-1, stress response (4)	2.5
ELF-1	AW503166			ets domain factor, expressed in lymphoid and epithelial tissues (5)	2.4
Ring finger protein 3 (RNF3)	AA403225		↑ [†]	homolog of 73Ah regulator of <i>Drosophila</i>	2.3
Homolog of Drosophila muscleblind B protein (MBLL)	AF061261			C3H-type zinc finger protein	2.3
SOX9/SRY (sex-determining region Y)	NM_000346			HMG domain, retinoid-inducible (6), involved in chondrocyte differentiation (7),	2.2
Sjogren syndrome antigen A2 (60kD, ribonucleoprotein SS-A/Ro)	U44388			Putative transcription regulator	2.1
Core promoter element binding protein (CPBP/ZF9/KLF8)	AL037865			Kruppel-like family transcription factor, activates keratin-4 promoter (8)	2
Growth inhibitors, intracellular					
p21 (Waf1/Cip1/Sdi1)	AA481712	↑ (9)		Pleiotropic inhibitor of cyclin-CDK complexes, inhibits or stimulates various transcription factors and cofactors (10)	5.1
Epithelial Protein Lost in Neoplasms (EPLIN)	AL048161			Decreased in multiple carcinomas (11)	3.5
B-cell translocation gene 1 (BTG1)	AI560266			Tumor suppressor (12)	2.8
B-cell translocation gene 2 (BTG2)	NM_006763	↑ (13)		BTG1-related growth inhibitor (13)	2.1
WIP1	NM_003620	↑ (14)		p53-inducible protein phosphatase (14)	2
Growth inhibitors, secreted					
Maspin	AA316156, AI435384	↑ (15)		Serine protease inhibitor, down-regulated in neoplasms, inhibits tumor growth, metastasis, angiogenesis (16), up-regulated in aging (17)	5.2, 3.3 [§]
MIC-1 (Prostate differentiation factor, PTGF-β, PLAB)	AB000584	↑ (18)		TGF-β family, down-regulated in cancers, induces growth arrest and apoptosis (19)	2.9
Insulin-like growth factor binding protein 6 (IGFBP-6)	AA675888			Retinoid-inducible (20)	2.7
Amphiregulin	NM_001657			EGF/TGF-β family secreted factor, promotes growth of normal epithelial cells but inhibits carcinomas (21), WT1-inducible (22)	2.3
Other growth regulators					

CD44 antigen	X66733, X55150			Adhesion molecule, growth modulator (23), up-regulated in aging (17)	3.9, 2.1 [§]
Jagged-1	U61276			Notch ligand, stem cell growth, angiogenic factor (24)	2
Cyclin D1 (Bcl-1)	M73554, X59798	↑ (25)	↑ (25)	G1/S transition; coregulated with p21 in cancers (26)	2.8, 2.2 [§]
Serum-inducible kinase (Snk, polo-like)	NM_006622			Putative cell growth regulator	2.2
Mitogenic/antiapoptotic factors, secreted					
CYR61	Y12084			Mitogenic/angiogenic factor (27)	3.3
Prosaposin	J03015		↑ (28)	Antiapoptotic/mitogenic (29) up-regulated in aging (30)	2.3
Transforming growth factor α (TGFα)	X70340	↑ (31)		EGF-related mitogen (32)	2
Proteases					
Kallikrein 7 (serine protease 6)	L33404			Up-regulated in ovarian carcinoma (33)	3.2
Calpain-L2	M23254				2.3
Neurosin (serine protease 9, Zyme, Protease M)	NM_002774			Down-regulated in breast cancers (34), up-regulated in ovarian carcinoma (35)	2
Plasminogen activator, urokinase	D11143				2
Cell adhesion and cell-cell contact					
P-cadherin	NM_001793			Lost in prostate cancer (36)	2.9
Desmoplakin (DPI, DPII)	J05211			Decreased in neoplasms (37), up-regulated in aging (38)	2.4
PM5 protein (collagenase-related)	X57398			Homologous to cell adhesion proteins	2.2
CD63/ME491 antigen	X62654				2.1
Mac-2 binding protein	X79089		↑ (28)	ECM organizer (39)	2
Occludin	U53823			Tight junction protein	2.1
ECM receptors					
Integrin β4	X53587				2.6
Laminin, α 3 (nicein/kalinin/BM600/epilegrin)	L34155				2.4
Syndecan 4 (amphiglycan, ryudocan)	D79206, NM_002999			Involved in wound repair and angiogenesis (40)	2.3, 2.2 [§]
Integrin α 6	X53586				2.2
Transmembrane signaling					
AHNAK nucleoprotein (desmoyokin)	M80899			Activates PLC- γ (41), decreased in neuroblastomas (42)	2.1
CD24 antigen	AI745625			Mucin-like glycoprotein, up-regulated in breast carcinoma (43)	2.1
Lipocortin-2 (annexin A2)	W53011			Substrate of src tyrosine kinase	2
Ion transport and ion exchange					
Phospholemman-like, 8 kD (MAT-8)	AA826766			Chloride channel activator	2.3
Ferritin, heavy polypeptide 1	AW575826		↑ [†]	Iron storage	2.8
Caveolin 2	AI093287			Membrane compartmentalization	2.2
Neurogranin	Y09689		↑ [†]	Calmodulin binding protein, neural	2.2
H1 chloride channel	AI381979			Colocalizes with caveolin (44)	2
Intracellular trafficking, cytoskeletal and scaffolding					
Interferon-induced protein 56 (IFI-56K/P56)	NM_001548			Tetratricopeptide protein, Int6 interaction (45)	3.2
Major vault protein (lung	X79882			Stress response, multidrug resistance	2.4

resistance protein, LRP)					
Macrophin (microfilament and actin filament cross-linker protein)	AB029290			Cytoskeletal	2.4
Microtubule-associated protein 1B (MAP1B)	L06237			Cytoskeletal, CK2 substrate	2
Proapoptotic					
NOXA	D90070	↑ (46)		Bcl2 family member (46)	2.7
Fas antigen/APO-1	M67454	↑ (47)		Apoptotic signal receptor	2.3
Keratins					
Keratin 18	X12881			Antiapoptotic (48)	4
Keratin 8	X74929	↑ (49)		Antiapoptotic (48)	3.4
Keratin 2A	AF019084				2.9
Keratin 7	M13955, AA307373				2.6 2.1 [§]
Keratin 15	NM_002275				2.3
Keratin 6B	L42611				2.1
Other					
High mobility group protein HMG2 homolog	AI191623				5.4
U1 small ribonucleoprotein 1SNRP homolog	AI400786				3.7
Retinaldehyde dehydrogenase 3 (ALDH6/RALDH3)	U07919			Retinoic acid synthesis	3.2
Tumor differentially expressed 1 (TDE1)	NM_006811			Transmembrane protein, homologous to mouse gene increased in testicular tumors (50)	2.4
Amyloid beta (A4) precursor protein (βAPP)	X06989		↑ (28)	Alzheimer's disease amyloid precursor	2
Integral membrane protein 2B (BR1/ITM2B)	AW131784			Amyloid precursor in familial British dementia (51)	2
Apolipoprotein E	K00396			Alzheimer's, atherosclerosis	2
Incyte EST	X62654				2.1
23815 human mRNA	U90916				2.1

*Known changes in gene expression after ectopic overexpression of p53 or p21.

†Effects of p21 induction in HT1080 fibrosarcoma cells, as determined by microarray hybridization (our unpublished data, not included in the original report; ref. 28).

‡BDE, balanced differential expression (from Incyte UniGEM V 2.0 hybridization analysis), in almost all cases underestimates the actual fold difference observed by RT-PCR.

§Two clones in the array were found to be derived from the same gene. The BDE values for both clones are shown

1. Reimold, A. M., Etkin, A., Clauss, I., Perkins, A., Friend, D. S., Zhang, J., Horton, H. F., Scott, A., Orkin, S. H., Byrne, M. C., *et al.* (2000) *Genes Dev.* **14**, 152–157.

2. Hai, T., Wolfgang, C. D., Marsee, D. K., Allen, A. E. & Sivaprasad, U. (1999) *Gene Expression* **7**, 321–335.

3. Wolfgang, C. D., Liang, G., Okamoto, Y., Allen, A. E. & Hai, T. (2000) *J. Biol. Chem.* **275**, 16865–16870.
4. Bohmann, D., Bos, T. J., Admon, A., Nishimura, T., Vogt, P. K. & Tjian, R. (1987) *Science* **238**, 1386–1392.
5. Bassuk, A. G., Barton, K. P., Anandappa, R. T., Lu, M. M. & Leiden, J. M. (1998) *Mol. Med.* **4**, 392–401.
6. Marshall, O. J. & Harley, V. R. (2000) *Mol. Genet. Metab.* **71**, 455–462.
7. Huang, W., Chung, U. I., Kronenberg, H. M. & de Crombrugge, B. (2001) *Proc. Natl. Acad. Sci. USA* **98**, 160–165. (First Published December 19, 2000; 10.1073/pnas.011393998)
8. Okano, J., Opitz, O. G., Nakagawa, H., Jenkins, T. D., Friedman, S. L. & Rustgi, A. K. (2000) *FEBS Lett.* **473**, 95–100.
9. El Deiry, W. S., Tokino, T., Velculescu, V. E., Levy, D. B., Parsons, R., Trent, J. M., Lin, D., Mercer, W. E., Kinzler, K. W. & Vogelstein, B. (1993) *Cell* **75**, 817–825.
10. Dotto, G. P. (2000) *Biochim. Biophys. Acta* **1471**, M43–M56.
11. Maul, R. S. & Chang, D. D. (1999) *Oncogene* **18**, 7838–7841.
12. Rouault, J. P., Rimokh, R., Tessa, C., Paranhos, G., Ffrench, M., Duret, L., Garoccio, M., Germain, D., Samarut, J. & Magaud, J. P. (1992) *EMBO J.* **11**, 1663–1670.
13. Rouault, J. P., Falette, N., Guehenneux, F., Guillot, C., Rimokh, R., Wang, Q., Berthet, C., Moyret-Lalle, C., Savatier, P., Pain, B., *et al.* (1996) *Nat. Genet.* **14**, 482–486.
14. Fiscella, M., Zhang, H., Fan, S., Sakaguchi, K., Shen, S., Mercer, W. E., Vande Woude, G. F., O'Connor, P. M. & Appella, E. (1997) *Proc. Natl. Acad. Sci. USA* **94**, 6048–6053.
15. Zou, Z., Gao, C., Nagaich, A. K., Connell, T., Saito, S., Moul, J. W., Seth, P., Appella, E. & Srivastava, S. (2000) *J. Biol. Chem.* **275**, 6051–6054.
16. Domann, F. E., Rice, J. C., Hendrix, M. J. & Futscher, B. W. (2000) *Int. J. Cancer* **85**, 805–810.
17. Lee, C. K., Weindruch, R. & Prolla, T. A. (2000) *Nat. Genet.* **25**, 294–297.
18. Tan, M., Wang, Y., Guan, K. & Sun, Y. (2000) *Proc. Natl. Acad. Sci. USA* **97**, 109–114.

19. Li, P. X., Wong, J., Ayed, A., Ngo, D., Brade, A. M., Arrowsmith, C., Austin, R. C. & Klamut, H. J. (2000) *J. Biol. Chem.* **275**, 20127–20135.
20. Dailly, Y. P., Zhou, Y., Linkhart, T. A., Baylink, D. J. & Strong, D. D. (2001) *Biochim. Biophys. Acta* **1518**, 145–151.
21. Plowman, G. D., Green, J. M., McDonald, V. L., Neubauer, M. G., Disteché, C. M., Todaro, G. J. & Shoyab, M. (1990) *Mol. Cell Biol.* **10**, 1969–1981.
22. Lee, S. B., Huang, K., Palmer, R., Truong, V. B., Herzlinger, D., Kolquist, K. A., Wong, J., Paulding, C., Yoon, S. K., Gerald, W., *et al.* (1999) *Cell* **98**, 663–673.
23. Herrlich, P., Morrison, H., Sleeman, J., Orian-Rousseau, V., König, H., Weg-Remers, S. & Ponta, H. (2000) *Ann. N. Y. Acad. Sci.* **910**, 106–118.
24. Walker, L., Lynch, M., Silverman, S., Fraser, J., Boulter, J., Weinmaster, G. & Gasson, J. C. (1999) *Stem Cells* **17**, 162–171.
25. Chen, X., Bargonetti, J. & Prives, C. (1995) *Cancer Res.* **55**, 4257–4263.
26. de Jong, J. S., van Diest, P. J., Michalides, R. J. & Baak, J. P. (1999) *Mol. Pathol.* **52**, 78–83.
27. Babic, A. M., Kireeva, M. L., Kolesnikova, T. V. & Lau, L. F. (1998) *Proc. Natl. Acad. Sci. USA* **95**, 6355–6360.
28. Chang, B. D., Watanabe, K., Broude, E. V., Fang, J., Poole, J. C., Kalinichenko, T. V. & Roninson, I. B. (2000) *Proc. Natl. Acad. Sci. USA* **97**, 4291–4296.
29. Hiraiwa, M., Taylor, E. M., Campana, W. M., Darin, S. J. & O'Brien, J. S. (1997) *Proc. Natl. Acad. Sci. USA* **94**, 4778–4781.
30. Mathur, P. P., Mo, M. Y., Panzironi, C., Silvestrini, B., Bardin, C. W., Grima, J. & Cheng, C. Y. (1994) *Biochem. Mol. Biol. Int.* **34**, 1063–1071.
31. Shin, T. H., Paterson, A. J. & Kudlow, J. E. (1995) *Mol. Cell Biol.* **15**, 4694–4701.
32. Kumar, V., Bustin, S. A. & McKay, I. A. (1995) *Cell Biol. Int.* **19**, 373–388.
33. Tanimoto, H., Underwood, L. J., Shigemasa, K., Yan Yan, M. S., Clarke, J., Parmley, T. H. & O'Brien, T. J. (1999) *Cancer* **86**, 2074–2082.
34. Anisowicz, A., Sotiropoulou, G., Stenman, G., Mok, S. C. & Sager, R. (1996) *Mol. Med.* **2**, 624–636.
35. Tanimoto, H., Underwood, L. J., Shigemasa, K., Parmley, T. H. & O'Brien, T. J. (2001) *Tumour Biol.* **22**, 11–18.

36. Jarrard, D. F., Paul, R., van Bokhoven, A., Nguyen, S. H., Bova, G. S., Wheelock, M. J., Johnson, K. R., Schalken, J., Bussemakers, M. & Isaacs, W. B. (1997) *Clin. Cancer Res.* **3**, 2121–2128.
37. Hiraki, A., Shinohara, M., Ikebe, T., Nakamura, S., Kurahara, S. & Garrod, D. R. (1996) *Br. J. Cancer* **73**, 1491–1497.
38. Ly, D. H., Lockhart, D. J., Lerner, R. A. & Schultz, P. G. (2000) *Science* **287**, 2486–2492.
39. Sasaki, T., Brakebusch, C., Engel, J. & Timpl, R. (1998) *EMBO J.* **17**, 1606–1613.
40. Echtermeyer, F., Streit, M., Wilcox-Adelman, S., Saoncella, S., Denhez, F., Detmar, M. & Goetinck, P. (2001) *J. Clin. Invest.* **107**, R9–R14.
41. Sekiya, F., Bae, Y. S., Jhon, D. Y., Hwang, S. C. & Rhee, S. G. (1999) *J. Biol. Chem.* **274**, 13900–13907.
42. Shtivelman, E., Cohen, F. E. & Bishop, J. M. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 5472–5476.
43. Fogel, M., Friederichs, J., Zeller, Y., Husar, M., Smirnov, A., Roitman, L., Altevogt, P. & Sthoeger, Z. M. (1999) *Cancer Lett.* **143**, 87–94.
44. Edwards, J. C. (1999) *Am. J. Physiol.* **276**, F398–F408.
45. Guo, J. & Sen, G. C. (2000) *J. Virol.* **74**, 1892–1899.
46. Oda, E., Ohki, R., Murasawa, H., Nemoto, J., Shibue, T., Yamashita, T., Tokino, T., Taniguchi, T. & Tanaka, N. (2000) *Science* **288**, 1053–1058.
47. Muller, M., Wilder, S., Bannasch, D., Israeli, D., Lehlbach, K., Li-Weber, M., Friedman, S. L., Galle, P. R., Stremmel, W., Oren, M., *et al.* (1998) *J. Exp. Med.* **188**, 2033–2045.
48. Caulin, C., Ware, C. F., Magin, T. M. & Oshima, R. G. (2000) *J. Cell Biol.* **149**, 17–22.
49. Mukhopadhyay, T. & Roth, J. A. (1996) *Anticancer Res.* **16**, 105–112.
50. Bossolasco, M., Lebel, M., Lemieux, N. & Mes-Masson, A. M. (1999) *Mol. Carcinog.* **26**, 189–200.
51. Vidal, R., Frangione, B., Rostagno, A., Mead, S., Revesz, T., Plant, G. & Ghiso, J. (1999) *Nature (London)* **399**, 776–781.